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A comparison of different measures of Respiratory Muscle Strength as Predictive Biomarkers for Survival in Amyotrophic Lateral Sclerosis

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~~**Respiratory Muscle Strength as Predictive Biomarker for Survival in Amyotrophic Lateral Sclerosis**~~

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Author contribution

All authors contributed to the concept of the study, critically reviewed the manuscript and approved this submission for publication. In addition, we note the following contributions: RL made the original measurements and reviewed the source data to create the material for the present analysis, KY and EJ undertook statistical analysis of the survival data to provide the analysis results for this paper, MIP reviewed the source data with RL to create the material for the present analysis and prepared the first and subsequent draft of the manuscript and PNL and JM were supervisors for the neurological and respiratory muscle aspects respectively of the original data collection.

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At a Glance Commentary

Scientific Knowledge on the Subject

While respiratory muscle weakness is known to be associated with a poor prognosis in amyotrophic lateral sclerosis (ALS), there are no comprehensive data which compare the prognostic power of different tests of inspiratory and expiratory muscle function at different time intervals. However, such data would facilitate enrichment of phase IIa studies of novel agents aiming to reduce mortality in ALS.

What This Study Adds to the Field

In a cohort of ALS patients followed until 100% mortality occurred, invasive and non-invasive tests of respiratory muscle strength were performed, allowing the predictive power for death or non-invasive ventilation of each test at time intervals up to three years to be assessed and for relevant cut-off points to be obtained. The best performing tests were sniff and twitch transdiaphragmatic pressure, but maximal sniff nasal inspiratory pressure also had excellent predictive power; SNIP values of 52, 71 85 and 88 cm H_2O displayed >95% sensitivity for ventilation free survival at 6,12,24 and 36 months respectively. While vital capacity also had good predictive power, the cut-off point indicating a poor prognosis was

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Abstract

Rationale: Biomarkers for survival in amyotrophic lateral sclerosis (ALS) would facilitate the development of novel drugs. Although respiratory muscle weakness is a known predictor of poor prognosis, a comprehensive ~~assessment of the power of respiratory~~comparison of different tests is lacking.

Objectives: To compare the predictive power of invasive and non-invasive respiratory muscle strength assessments for survival or ventilator-free survival, up to three years.

Methods and Measurements: ~~Respiratory~~ From a previously published report respiratory muscle strength measurements were available for 78 ALS patients. Time to death and/or ventilation were ascertained. Receiver operating characteristic analysis was used to determine the cut-off point of each parameter.

Main Results: Each respiratory muscle strength assessment individually achieved statistical significance for prediction of survival or ventilator-free survival. In multi-variate analysis ~~only~~ sniff transdiaphragmatic ~~and oesphageal~~ pressure (Sn Pdi ~~and Sn Poes~~), twitch transdiaphragmatic pressure (Tw Pdi) and maximal static expiratory mouth pressure (MEP) ~~retained~~ were ~~significance~~ significant ~~for~~ predictors of ventilation-free survival and Tw Pdi and MEP for absolute survival.

While all measures had good specificity, there were widely differing sensitivities. All cut-off points for the vital capacity (VC) were >80% of normal, except for prediction of three month outcomes. Sequential data showed a linear decline for direct measures of respiratory muscle strength, whereas VC showed little to no decline until 12 months prior death/ventilation.

Conclusions: The most powerful biomarkers for mortality stratification in ALS ~~were~~ was Tw Pdi ~~and Sn Pdi~~, but the predictive power of sniff nasal inspiratory pressure was also excellent. A VC within normal range suggested a good prognosis ~~during~~ at three months but ~~is~~ was of little other value.

Keywords: Amyotrophic Lateral Sclerosis, survival, diaphragm, maximal inspiratory pressure, sniff nasal inspiratory pressure

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive and devastating neurological condition characterised by progressive muscle weakness. Although riluzole is licensed for ALS treatment~~-~~ (1)~~[1]~~, the benefits in clinical practice have proved modest and new drugs are urgently required. ALS-related respiratory muscle weakness is relatively uncommon at presentation, but ~~type II~~hypercapnic respiratory failure due to muscle weakness is common in established ALS. Although non-invasive ventilation (NIV) is an effective therapy, especially for patients with non-bulbar disease (2, 3)~~[2]~~, it comes with both a poorer prognosis and the inconvenience of wearing a ventilator apparatus; therefore, it may be considered a 'hard' adverse endpoint.

For most conditions, including ALS, trials powered to detect improvements in survival are expensive. This may delay the evaluation and introduction of new drugs or technologies (e.g. diaphragm pacing). Therefore biomarkers, either as a surrogate outcome measure or as a stratification tool, would be useful to enrich the study population for those at high risk of meeting the endpoint. In ALS, mortality or the need for ventilator support are objective endpoints which additionally have obvious validity to patients, regulators and payers.

Several studies have identified respiratory muscle weakness, measured directly or as vital capacity (VC), as a predictor of daytime respiratory failure (4) or death (5-7). Respiratory muscle strength could therefore be a valuable biomarker. However, there are some gaps in the literature diminishing the value of current data. Firstly, the literature disproportionately depends on VC as measure of respiratory muscle strength. Whilst VC has some advantages (e.g. widespread availability), the relationship of directly measured respiratory muscle strength with VC is, as expected from the pulmonary pressure volume curve ~~[8]~~ (8), not linear (9) ~~[9]~~. Therefore it is unknown whether VC is responsive to disease progression throughout the entire disease course. Secondly, no large-scale study has compared the prognostic power of direct measurement of diaphragm function as transdiaphragmatic pressure with non-invasive measures. Thirdly, the prognostic value of non-volitional measures of respiratory muscle function have not been evaluated, with the exception of Pinto *et al*, who undertook phrenic nerve stimulation (10) ~~[10]~~. However, they used an electrical technique, which can be unreliable even in experienced hands (11) ~~[11]~~, and used the compound muscle action potential as outcome measure rather than a measure of force. Lastly, most studies are limited by the lack of sequential data and a short follow-up, leaving a proportion of the participants alive thus diminishing statistical power ~~due to the large portion of the population still alive at the time of analysis.~~ .

Between 1996 and 2000, we studied (4) a large group of ALS patients (N=81) using invasive and non-invasive measures of respiratory muscle function (12) ~~[12] of respiratory muscle function [3]~~; however our prior publication presented only cross-sectional data and explored the relationship between respiratory muscle strength and both daytime and nocturnal hypercapnia. In the current analysis, conducted between 2014-2015, the value of these measures for the prediction of death or initiation of NIV were assessed.

Methods

Participants

The present study used respiratory muscle function data from a previously published ALS patient cohort, containing 81 patients (16 females) studied between 1996-2000 (4) ~~[3]~~. Entry into the study was not dependent on the presence or absence of respiratory symptoms. The date of death was ascertained in 2014, using both hospital and central NHS records. Treatment with NIV was obtained from the clinical records, where available.

Participants were recruited from the King's MND Care and Research Centre, where a diagnosis of ALS was confirmed by a consultant with a special interest in ALS and classified as El Escorial 'Possible, probable or definite' (13) ~~[13]~~. The study was approved by the Kings College Hospital ethics committee and all patients provided written informed consent.

Measurements

At the time of assessment, none of the patients had received ventilatory support, although several were subsequently treated with non-invasive positive-pressure ventilation. The respiratory muscle strength measurement protocol has been described previously (4) ~~[14]~~. The following parameters were included: VC, maximal static inspiratory and expiratory mouth pressures (MIP and MEP, respectively), maximal sniff nasal inspiratory pressure (SNIP), maximal sniff oesophageal (Sn Poes) and transdiaphragmatic pressures (Sn Pdi), unpotentiated twitch transdiaphragmatic pressure (Tw Pdi) using cervical magnetic stimulation ~~[15]~~ (14, 15), maximal cough gastric pressure (Cough Pga) (16) ~~[16]~~ and the unpotentiated twitch abdominal pressure elicited by magnetic stimulation of the 10th thoracic intervertebral space (Tw T10) (17) ~~[17]~~.

Statistical analysis

A stepwise selection method using Cox regression was performed to determine the relationship between each variable and both survival and ventilation-free survival. Following variables were included in the stepwise regression analysis: Tw Pdi (cm H_2O), Sn Pdi (cm H_2O) Sn Poes (cm H_2O), SNIP (cm H_2O), SNIP (percent-predicted), VC (percent-predicted), MIP (cm H_2O), MIP (percent-predicted), MEP (cm H_2O), MEP (percent-predicted), Cough Pga (cm H_2O), age and gender. The stepwise selection significance levels for entering and removing were 0.2 and 0.1, respectively. Sensitivity and specificity analyses, for the prediction of survival and ventilation-free survival, were performed for each parameter at three-monthly intervals until 18 months and thereafter at six-monthly intervals until the third year. Furthermore, the relationship of the strongest predictors from the multi-variate analysis model with non-invasive measures of respiratory muscle strength were investigated.

The values derived from the receiver operating characteristic (ROC) plot, offering the greatest sensitivity and sensitivity as a function of time, were plotted for each parameter. Kaplan-Meier survival analyses were performed, correlating death or the date of initiation of NIV for each parameter, with three groups based on normal values for each test; these were ≥80%-predicted (i.e. within the normal range), 45-<80%-predicted and <45%-predicted.

For patients in whom multiple measures were available, graphical plots were used to determine the trajectory of each parameter prior to death.

Results

After review of the source (paper) data (4)~~[3]~~ and the date of death, 78 patients (17 females) were included. Only 21.8% of the sample were women; this was not the result of any deliberate recruitment bias and compares with an overall clinical population with a male:female ratio of approximately 3:2.

Riluzole was taken by the majority of patients. The long time-interval between respiratory function measurement (1996-2000) and survival analysis (2014-2015) unfortunately ensured a 100% mortality rate in our cohort. The patients survived a mean 744 days from the date of inclusion in the previously published cohort (4) ~~[3]~~. NIV was offered to patients managed by our institution, but this was not universal practice in the United Kingdom at that time of the study. Therefore, NIV was not offered to some participants. In addition, due to the wide geographical referral base of the King's MND Care and Research Centre, NIV data could not be obtained for some (N=9) cases.

The mean (standard deviation [SD]) age of the included patients was 61 (8.7) years and they had a mean (SD) ALS functional rating score of 28 (6), a mean (SD) Norris limb score of 41 (12.9) out of 63, and a mean Norris bulbar score of 34 (8.5) out of 39 (Table 1). As expected and as shown in Table 1, a range of respiratory muscle weakness was observed in the patient population; inherent to the condition not all patients had the stamina to complete all the tests and where so we opted to prioritise respiratory muscle tests; numbers for the datasets available for each parameter is also given in table 1~~.~~

Predictive value of respiratory muscle strength tests for death and non-invasive ventilation

A stepwise regression analysis was performed in all patients who had complete data (N=57) for all tested variables (Tw Pdi, Sn Pdi, Sn Poes, SNIP, VC, MIP, MEP and Cough Pga, age and gender).

In the stepwise regression analysis for ventilation-free survival (Table 2A), all respiratory muscle strength assessments achieved statistical significance (P<0.05) in their individual score tests, whereas no significance was observed for gender (P=0.83) or age (P=0.81). Sn Pdi and Tw Pdi had the highest values in the individual score tests, whereas the lowest values were registered for age and gender. In the final multi-variate analysis model for ventilation-free survival, five variables retained significance: age (p=0.0027), Tw Pdi (P<0.0001), Sn Pdi (P=0.0025), Sn Poes (P=0.0275) and MEP %-predicted (P=0.0544) (Table 2B).

In the stepwise regression analysis for absolute survival (Table 2A), each respiratory muscle strength assessment achieved statistical significance (P<0.05) in their individual score tests, whereas no significance was observed for gender (P=0.68) or age (P=0.11). The highest values in the individual score tests were observed for Sn Pdi and Tw Pdi, whereas the lowest values were registered for gender and age. In the final analysis model for absolute survival, two variables retained significance: Tw Pdi (P=0.0018) and MEP (P=0.0073) (Table 2B).

The sensitivity and specificity of the key non-invasive (VC, SNIP, MIP and MEP) and invasive (Tw Pdi and Sn Pdi) respiratory muscle strength measures to predict death or the use of NIV as a function of time prior to that event and at time points up to 3 years are shown in Table 3, and Table E2 for the MEP. The cut-off values and area under the curve, identified from the ROC analysis by visual analysis, as a function of time prior to that event and at time points up to 3 years are shown in Figures 1 and ~~2~~E1, respectively. ROC analyses showed AUC >0.8 at most time-points for all tests, but the numerical range of cut-off points varied. It should be noted that while all measures had good to excellent specificity, there were widely differing sensitivities for the prediction of death or ventilator use. The VC value which gave the best 'cut-off point' was higher than 80%-predicted at all time-points, except for outcome prediction at three months.

Figure ~~3~~ 2 shows the Kaplan-Meier survival curves for the three principle techniques (VC, SNIP and MIP) used for non-invasive assessment of inspiratory muscle strength. For each parameter, the participants were categorised into the following subgroups: ≥80%-predicted (i.e. within the normal range), 45 to <80%-predicted and <45%-predicted. Although, a result within the normal range was associated with the longest survival for all three non-invasive inspiratory muscle strength parameters, VC discriminated less between moderate and severe weakness compared to SNIP and MEP.

Sequential measures of respiratory muscle strength were obtained for only 25 participants on 2 to 11 occasions either because it was impractical for the majority of the visits or the patient declined to participate. Figure 3 shows the serial behaviour of respiratory muscle strength parameters in those 25 patients in whom serial measures were available. The VC declined slowly until 12 months prior to death, followed by a rapid decline until death. In contrast, a more linear pattern was observed for direct measures of respiratory muscle strength, including SNIP (%-predicted), Sniff Pdi (cm H_2O), Twi pdi (cm H_2O), MIP (%-predicted) and MEP (%-predicted).

A correlation of Tw Pdi with Sn Pdi and with non-invasive measures of respiratory muscle strength, including MIP, SNIP and VC, was observed (Figure ~~5~~4).

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For most conditions, trials powered to detect improvements in survival are expensive. This may delay the evaluation and introduction of novel drugs or technologies aiming to reduce mortality. Therefore biomarkers, either as a surrogate outcome or as a stratification tool, would be useful to enrich trials for those at high risk of meeting the study endpoint.

Critique of the Method

Each respiratory muscle strength assessment individually achieved statistical significance for prediction of death or ventilator-free survival. These findings are in line with previous studies, reporting that respiratory muscle strength measures are strong predictors of death or the need to use NIV. Our study did not evaluate all tests of respiratory muscle function or questionnaires such as the SINQ-5 (18); in particular supine vital capacity has been identified as a sensitive marker of isolated diaphragm dysfunction in ALS {Lechtzin, 2002 #4594}; this test is attractive in the sense that spirometry is widely available but we caution that many ALS patients cannot easily transfer on to a testing couch especially as the condition progresses, and its prognostic value remains unknown. Other techniques of reported value for assessment of respiratory muscle function in ALS include measurement of compound muscle action potential elicited by phrenic nerve stimulation {Jenkins, 2016 #4597}{Pinto, 2012 #4598}, but since this was not measured in the current study we are unable to comment on its value in comparison to measurement of force as Pdi

We also acknowledge that our analysis is strictly confined to indices of respiratory muscle function. Thus we have deliberately not sought to confirm whether a bulbar presentation is associated with a poor prognosis which has been explored in larger studies. Similarly nocturnal hypoventilation which is known to be associated with a poor prognosis was not explored in this analysis, at least in part because most authorities now consider this to be an indication for NIV. Finally we are aware that sequential measures, particularly when used in conjunction with sophisticated modelling techniques as described by Carreiro and co-workers {Carreiro, 2015 #4596}, may be offer an alternative predictive strategy. However, particular for the purposes of recruiting to clinical trials, or counselling patients it is often preferable to base a decision on a single measurement

The current cohort is not sufficiently powerful to dissect factors predictive of death once NIV has been established. Even if it had been, it could not have accommodated other aspects of ventilator support which are culturally influenced ref, such as the use of 24-hour tracheostomy ventilation (T-IPPV) ~~[24]~~. It is anecdotally accepted that ALS patients receiving T-IPPV and enteral feeding, live longer and may die for reasons other than ALS (19) ~~[25]~~; unsurprisingly the overall burden of disease involvement may be predictive in T-IPPV users (20) ~~[26]~~.

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Although the cohort is, to our knowledge, the largest ALS cohort to have had invasive measures of respiratory muscle strength, only limited serial non-invasive respiratory muscle strength data were available.

The choice of death or NIV use as endpoint requires defence, especially as the patients were studied when NIV was being introduced as a therapeutic option for ALS in the United Kingdom. While all patients at the King's Centre were considered for NIV as appropriate, this may not have applied to other referring centres. This issue was confirmed by a pooled analysis of 2,477 ALS patients participating in three (negative) therapeutic trials reported between 2004 and 2006 (21) ~~[18]~~, a similar period to the time at which the respiratory muscle strength measurements were made in the current study. Unsurprisingly, variation in ventilation practice was reported between countries and at different institutions within the same country, with ventilator interventions ranging from 0% to 23.1%. Due to this variation, a larger sample size was required for the study of composite endpoints compared to death alone. However, the practical arguments in favour of the composite endpoint of death or ventilation from a drug development perspective are first that ventilation itself represents a considerable healthcare burden and second that, since ventilation itself increases longevity (2) ~~[27]~~, the use of NIV might obscure a true treatment effect of a novel therapeutic agent.

Significance of the findings

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Although respiratory muscle weakness is known as a poor prognostic feature in ALS (4-7) and other neuromuscular disorders, such as the muscular dystrophies or Pompe disease, there are no comprehensive data which compare the prognostic power of different tests of inspiratory and expiratory muscle function at different time intervals in any condition. Therefore, the current study assessed the value of non-invasive and invasive respiratory muscle strength assessments, at different time points up to three years, for the prediction of death or the initiation of NIV in a large cohort of ALS patients (N=78).

Sn Pdi and Twi Pdi were the best performing tests for prediction of ventilator-free survival, but SNIP also had excellent predictive power. Although VC also had good predictive power for ventilation-free survival, the cut-off value indicating a poor prognosis was within the normal range (i.e. >80%-predicted) for all time intervals beyond three months, making this a less useful stratification variable for most studies. In addition, in a longitudinal subset of our cohort the inferiority of VC for enrichment against an endpoint of ventilator-free survival was observed. This is in line with findings from a pooled analysis (in 2,477 ALS patients) reporting that relatively high VC values may be observed close to a clinical meaningful event (e.g. tracheostomy) (21). In that study, VC measurements were available for 50 ALS patients requiring tracheostomy within 30 days of the need for tracheostomy, and were 50% or more of the predicted value in 11 patients, 60% or more of the predicted value in seven patients, and 70% or more of the predicted value in five patients ~~[18]~~. Combined, these data suggest that VC is a poor tool for assessing change until the period immediately prior to death. In contrast to Sn Pdi, Twi Pdi and SNIP, for which linear declines were observed in the longitudinal cohort.

In the multi-variate analysis for absolute survival, Tw Pdi and MEP reached statistical significance. This confirms for the first time a modest, but measurable impact of expiratory muscle function on survival in AL~~S~~S~~, although not on ventilator-free survival~~. The predictive effect of MEP was substantially weaker than the predictive value of inspiratory muscle strength assessments, but was retained in multi-variate analysis, and is therefore not likely to be an epiphenomena. It has been previously reported that a profound expiratory muscle weakness is associated with the inability to generate transient supramaximal flow during a cough ~~[19]~~(22), which has been hypothesised to reduce defence against respiratory tract infection and aspiration. Impaired survival has been reported after NIV in those with mucous accumulation (23) ~~[20]~~; this perhaps points to the inability to satisfactorily expectorate mucous. The attenuation of the effect, considering ventilator free-survival, was likely due to the benefits of NIV in reducing the impact of chest infection both by improving blood gases but also by preventing basal atelectasis. This observation strengthens the case for further study of devices which facilitate expectoration of sputum (24, 25) ~~[21,22]~~.

The Tw Pdi may be considered a 'gold standard', because it is independent of patient motivation or tester aptitude (14). Our data confirm the expected relationship between volitional and non-invasive tests of inspiratory muscle function and the Tw Pdi. While Tw Pdi and Sn Pdi may be considered direct measures of diaphragm strength, Sn Poes and SNIP reflect overall inspiratory muscle strength; while the diaphragm does constitute the majority of inspiratory muscle function in normal humans it is clear that Sn Poes and Sn Pdi are not therefore measuring exactly the same quantity. In that context Table 2b is of interest since it will be noted that while much the strongest association with ventilation free survival was achieved by Tw Pdi, that the associations with Sn Pdi and Sn Poes were of opposite polarity so that while in univariate analysis a reduced Sn Poes was associated with reduced survival, in multivariate analysis an increased Sn Poes was statistically associated with a slightly increased risk of death or ventilation. We suspect this paradox occurs because disease impact on the non-diaphragmatic muscles (which is what Sn Poes captures once Pdi has been stratified for during the process of multivariate analysis) is a marker of wider regional involvement.

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In conclusion, the value of respiratory muscle strength as a biomarker is confirmed by the ~~present data~~current analysis. By providing detailed sensitivity and specificity predictions, the present data can be used to permit smaller sample sizes in future ALS trials and thus to permit a more rapid sorting of treatments into those with benefit and those without. While VC has a good sensitivity, the cut-off points identified by ROC analysis were largely within the normal range and our longitudinal data confirmed that change in VC was of small amplitude until close to death or the need for NIV. Our data suggest that direct measurement of respiratory muscle strength may be a more useful biomarker.

Acknowledgements

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References

FIGURE LEGENDS

Figure 1. Cut-off values of the respiratory muscle strength parameters with greatest sensitivity for prediction of time to death or non-invasive ventilation

Graphical analysis showing the cut-off point identified from the receiver operating characteristic (ROC) analysis for the prediction of death or non-invasive ventilation for the key respiratory muscle strength parameters as a function of time prior to that event

Tw Pdi: twitch transdiaphragmatic pressure, Sn Pdi: sniff transdiaphragmatic pressure, MIP: maximal static inspiratory mouth pressure, MEP: maximal static expiratory mouth pressure, VC: vital capacity, SNIP: sniff nasal inspiratory pressure

~~**Figure 2. Area under the curve of the respiratory muscle strength parameters with greatest sensitivity for prediction of time to death or non-invasive ventilation**~~

Figure ~~3~~2. Kaplan-Meier ~~survival~~ analysis (for the composite endpoint of death or NIV use) for the A) vital capacity (VC), B) sniff nasal inspiratory pressure (SNIP) and C) maximal static inspiratory mouth pressure (MIP)

The participants were categorised into three subgroups: ≥80%-predicted (i.e. within the normal range), 45-<80%-predicted and <45%-predicted. The p-values of log-rank tests of equality over subgroups are all <=0.0001

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Figure 3. Longitudinal respiratory muscle strength data in a subset of patients for whom sequential measures were available (N=25) for the A) vital capacity (VC), B) sniff nasal inspiratory pressure (SNIP), C) twitch transdiaphragmatic pressure Twi Pdi, D) sniff transdiaphragmatic pressure (Sn Pdi), E) maximal static inspiratory mouth pressure (MIP),

F) maximal static expiratory mouth pressure (MEP) and G) gastric pressure during maximal cough (Cough Pga)

Figure ~~5~~4. The correlation of twitch transdiaphragmatic pressure (Twi Pdi) with A) sniff transdiaphragmatic pressure (Sn Pdi), B) sniff nasal inspiratory pressure (SNIP), C) maximal static inspiratory mouth pressure (MIP) and D) vital capacity (VC)

Table 1: Demographic data of participants

	Score indicating normal function	N (of 78)	Mean	Standard deviation	Median	Q1, Q3
Demographics						
Age, years	-	78	61	8.7	61	55,66
Gender, male/female	-	78	61/17	-		
ALS FRS	40	56	28	5.6	29	23,32
Norris Limb	63	58	41	12.9	41.5	36,49
Norris Bulbar	39	58	34	8.5	35	30,39
MRC UL	60	48	53	7.5	55	46.5,59
MRC LL	40	48	33	8.7	37	28.5,40
MRC Neck	10	48	9	1.2	10	8.5,10
Respiratory muscle strength						
Tw Pdi, cm H_2O	>18 cm H_2O	76	15.0	12.7	9.9	5.7,23.9
Sn Pdi, cm H_2O	>70 cm H_2O	76	57.6	43.3	47	19.7,88.9
Sn Poes, cm H_2O	>60 cm H_2O	76	54.0	32.3	45	31.9,71
MIP, cm H_2O	-	75	36.2	26.0	28	18,47
MIP, %-predicted	-	75	43.6	29.2	35	21.2,63
MEP, cm H_2O	-	75	48.6	30.1	39	28,67
MEP, %-predicted	-	75	40.7	22.2	41.35	22.2,58
VC, %-predicted	-	74	71.5	27.6	68.5	50,97.8

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	Score indicating normal function	N (of 78)	Mean	Standard deviation	Median	Q1, Q3
SNIP, cm H_2O	>60 cm H2O	62	51.0	31.7	44	27.7,66
SNIP, %-predicted	-	62	52.8	30.8	44.85	27.9,76.75
Cough Pga, cm H_2O	-	75	91.8	61.0	83	42.25,121.8
Tw T10, cm H_2O	-	70	15.9	14.0	12	5.7,22

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Three individuals scored zero for some of the respiratory muscle strength assessments due to an inability to perform the manoeuvre.

ALS: Amyotrophic Lateral Sclerosis Functional Rating Scale, MRC UL: Medical Research Council Upper Limb, MRC LL: Medical Research Council Lower Limb, Tw Pdi: twitch transdiaphragmatic pressure, Sn Pdi: sniff transdiaphragmatic pressure, Sn Poes: sniff oesophageal pressure, MIP: maximal static inspiratory mouth pressure, MEP: maximal static expiratory mouth pressure, VC: vital capacity, SNIP: sniff nasal inspiratory pressure, Cough Pga: cough gastric pressure, Tw T10: twitch abdominal pressure elicited by magnetic stimulation of the 10th thoracic intervertebral space

Table 2: Stepwise regression for ventilation-free and absolute survival

A. Individual score test results

	Ventilation-free survival		Absolute survival	
Effect	**Chi-Square**	***P*-value**	**Chi-Square**	***P*-value**
Age, years	0.0556	0.8136	2.5544	0.1100
Gender	0.0458	0.8305	0.1746	0.6761
Tw Pdi, cm H_2O	47.9799	<0.0001	22.3576	<0.0001
Sn Pdi, cm H_2O	54.3358	<0.0001	21.3279	<0.0001
Sn Poes, cm H_2O	29.6091	<0.0001	20.0359	<0.0001
SNIP, cm H_2O	30.1857	<0.0001	19.7347	<0.0001
SNIP,%-predicted	34.5232	<0.0001	20.1526	<0.0001
VC,%-predicted	32.6306	<0.0001	16.8896	<0.0001
MIP, cm H_2O	21.9363	<0.0001	15.1205	0.0001
MIP, %-predicted	24.0194	<0.0001	14.3513	0.0002
Cough Pga, cm H_2O	15.4459	<0.0001	16.6363	<0.0001
MEP, cm H_2O	22.6263	<0.0001	19.5375	<0.0001
MEP, %-predicted	30.7708	<0.0001	19.0626	<0.0001

Tw Pdi: twitch transdiaphragmatic pressure, Sn Pdi: sniff transdiaphragmatic pressure, Sn Poes: sniff oesophageal pressure, MIP: maximal static inspiratory mouth pressure, MEP: maximal static expiratory mouth pressure, VC: vital capacity, SNIP: sniff nasal inspiratory pressure, Cough Pga: cough gastric pressure, Tw T10: twitch abdominal pressure elicited by magnetic stimulation of the 10th thoracic intervertebral space

B. Final multi-variate analysis model of maximum likelihood estimates

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Parameter	Parameter estimate	Standard error	Chi-Square	*P*-value	Hazard ratio	95% CI of Hazard ratio
Ventilation-free survival						
Age	-0.06332	0.02112	8.9861	0.0027	0.939	(0.901,0.978)
TwPdi, cm H_2O	-0.13279	0.03104	18.3039	<.0001	0.876	(0.824,0.931)
Sn Pdi, cm H_2O	-0.03014	0.00996	9.1576	0.0025	0.970	(0.952,0.989)
Sn Poes, cm H_2O	0.02091	0.00949	4.8578	0.0275	1.021	(1.002,1.040)
MEP, % predicted	-0.02138	0.01111	3.7003	0.0544	0.979	(0.958,1.000)
Absolute survival						
TwPdi, cm H_2O	-0.03754	0.01201	9.7724	0.0018	0.963	(0.941, 0.986)
MEP, cm H_2O	-0.01529	0.00570	7.1953	0.0073	0.985	(0.974, 0.996)

~~B.~~

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~~Parameter~~	~~Parameter estimate~~	~~Standard error~~	~~Chi-Square~~	~~*P*-value~~	~~Hazard ratio~~
~~Ventilation-free survival~~					
~~Age~~	~~-0.06332~~	~~0.02112~~	~~8.9861~~	~~0.0027~~	~~0.939~~
~~TwPdi, cm H_2O~~	~~-0.13279~~	~~0.03104~~	~~18.3039~~	~~<0.0001~~	~~0.876~~
~~Sn Pdi, cm H_2O~~	~~-0.03014~~	~~0.00996~~	~~9.1576~~	~~0.0025~~	~~0.970~~
~~Sn Poes, cm H_2O~~	~~0.02091~~	~~0.00949~~	~~4.8578~~	~~0.0275~~	~~1.021~~
~~MEP, %-predicted~~	~~-0.02138~~	~~0.01111~~	~~3.7003~~	~~0.0544~~	~~0.979~~
~~Absolute survival~~					
~~TwPdi, cm H_2O~~	~~-0.03754~~	~~0.01201~~	~~9.7724~~	~~0.0018~~	~~0.963~~
~~MEP, cm H_2O~~	~~-0.01529~~	~~0.00570~~	~~7.1953~~	~~0.0073~~	~~0.985~~

Tw Pdi: twitch transdiaphragmatic pressure, Sn Pdi: sniff transdiaphragmatic pressure, Sn Poes: sniff oesophageal pressure, MEP: maximal static expiratory mouth pressure

Table 3.

Receiver operating characteristic (ROC) analysis for key respiratory muscle strength parameters up to three years of follow-up for ventiulation free survival. Data for the MEP are shown in Table E2

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~~**Receiver operating characteristic (ROC) analysis for key respiratory muscle strength parameters up to three years of follow-up**~~

A. Non-invasive respiratory muscle strength parameters

	Vital capacity (%-predicted)				Sniff nasal inspiratory pressure (%-predicted)				Maximal static inspiratory mouth pressure (%-predicted)			
Projected time (months)	Cut-off	AUC	Sensitivity	Specificity	Cut-off	AUC	Sensitivity	Specificity	Cut-off	AUC	Sensitivity	Specificity
3	78	0.837	0.62	0.96	49	0.877	0.61	0.95	51	0.731	0.46	0.96
6	81	0.894	0.61	0.97	52	0.859	0.55	0.95	54	0.796	0.49	0.97
9	85	0.906	0.63	0.97	71	0.865	0.50	0.96	64	0.813	0.44	0.97
12	88	0.892	0.61	0.97	71	0.847	0.53	0.96	64	0.822	0.46	0.97
15	105	0.848	0.37	0.98	82	0.846	0.48	0.97	83	0.807	0.27	0.98
18	105	0.868	0.37	0.96	82	0.845	0.52	0.97	83	0.844	0.30	0.98

24	106	0.854	0.41	0.98	85	0.865	0.55	0.98	84	0.849	0.32	0.98
36	111	0.883	0.46	0.98	88	0.981	0.83	0.98	93	0.909	0.31	0.98

B. Invasive respiratory muscle strength parameters

	Twitch transdiaphragmatic pressure ($cm\ H_2O$)				Sniff transdiaphragmatic pressure ($cm\ H_2O$)			
Projected time (months)	**Cut-off**	**AUC**	**Sensitivity**	**Specificity**	**Cut-off**	**AUC**	**Sensitivity**	**Specificity**
3	9.8	0.913	0.78	0.96	47.1	0.926	0.74	0.96
6	17.0	0.919	0.60	0.97	47.1	0.951	0.82	0.97
9	17.0	0.962	0.69	0.97	55.0	0.976	0.85	0.97
12	18.6	0.943	0.70	0.98	77.2	0.963	0.65	0.98
15	26.1	0.943	0.47	0.98	89.0	0.950	0.60	0.98
18	26.1	0.938	0.52	0.98	89.0	0.952	0.67	0.98
24	28.4	0.922	0.45	0.98	103.0	0.933	0.59	0.98
36	28.4	0.958	0.77	0.98	108.5	0.978	0.85	0.98

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